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(54) Title: USE OF 1-HYDROXY-2-PYRIDONES FOR THE TREATMENT OF SKIN DISEASES

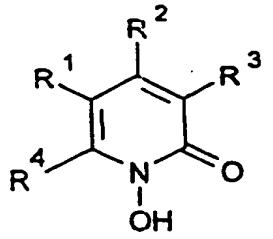
(54) Bezeichnung: VERWENDUNG VON 1-HYDROXY-2-PYRIDONEN ZUR BEHANDLUNG VON HAUTINFEKTIONEN

(57) Abstract

Compounds of the formula (I) are suitable for producing pharmaceuticals for topical treatment of skin diseases caused by fungi or bacteria.

(57) Zusammenfassung

Verbindungen der Formel (I) eignen sich zur Herstellung von Arzneimitteln zur topischen Behandlung von Hautinfektionen, die durch Pilze und Bakterien verursacht werden.



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Use of 1-hydroxy-2-pyridones for the treatment of skin infections

Infections of the skin are caused to a vast extent by skin-pathogenic bacteria or fungi. Their treatment - depending on the particular pathogen - is carried out either using antibacterial or using antimycotic agents.

Staphylococci and streptococci are a cause of bacterial infections of the skin in about 70% of all cases. Further important pathogens of bacterial skin infections which may be mentioned are Proteus sp. Other bacteria which grow under aerobic and anaerobic conditions, such as enterococci, Escherichia coli, Pseudomonas aeruginosa and Klebsiella come into question far less frequently as pathogens of skin infections.

Yeasts, on the other hand, have recently markedly gained in importance as pathogens of skin infections, in particular in immunosuppressed patients, in which the mucocutaneous and systemic spread of the yeasts can be a therapeutic problem.

Since bacteria as a rule have no noticeable keratinase activity, which is necessary for the start of an infection, fungal infections are frequently a starting point for the emergence of bacterial secondary infections.

The present invention therefore relates to substances which are suitable for the topical treatment both of fungal infections and of bacterial infections of the skin. Topical wide-spectrum antiinfectives according to the present invention were until now not available as monopreparations for the treatment of skin infections.

In the choice of agents for antibacterial therapy, inter alia, development of resistance must in particular be taken into consideration. Especially in the case of longer treatment, the pathogen spectrum should be determined by wound smears and its behavior checked with respect to the compositions used. Furthermore, note must be made of contact sensitivities and intolerability reactions. Especially in the case of neomycin and gentamycin,

which have been used for many years in the treatment of skin infections, the danger of sensitization is high.

For staphylococcal infections of the skin, which are frequent everywhere, erythromycin and clindamycin are frequently also employed in addition to gentamycin. They are used both locally, mainly in acne therapy, and also systemically.

However, owing to systemic administration, which has been carried out for many years, therapy-resistant bacterial strains have developed both against gentamycin and against erythromycin and clindamycin to a great extent - even against modern gyrase inhibitors, such as, for example, ofloxacin. In a retrospective study, Th. Forssmann et al. (H + G Volume 69, Part 12, 1994, pp. 828 - 832) analyzed the antibiotic resistance of Propionibacterium acnes and Staphylococcus epidermidis in acne patients who were pretreated with antibiotics.

The investigations show that, with respect to Propionibacteria, resistances were found to erythromycin in 36% and to clindamycin in 11% of the cases. With Staphylococcus epidermidis, resistances were found to erythromycin in 90% and to clindamycin in 40% of the cases.

The increasing number of resistances of enterococci to gentamycin (up to 50% in isolates from various centers) gives reason to think particularly the same strains also are resistant to many other substances, including vancomycin (Martindale 30th Edition, 1993, pp. 171,2).

The same problem exists with gentamycin-resistant Staphylococcus aureus strains, which as a rule are also insensitive to methicillin and ofloxacin (Martindale 30th Edition, 1993, pp. 171,2 own investigations).

It is furthermore known from the literature that among the conventional antibiotics cross-resistances are developing to an increasing extent. Thus, inter alia, in the case of patients who were only pretreated with

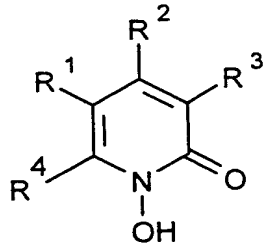
erythromycin, in 20% of the cases a resistance to clindamycin was also observed.

For the reasons outlined, it no longer applies as a therapeutic standard today also to employ topically antibiotics which are used systemically.

In the search for a new therapeutic standard for antibiotically active substances to be used topically, it has now surprisingly been found that substances from the 1-hydroxy-2-pyridone class, which until now have found their way into therapy exclusively as antimycotics, are also excellently suited for the topical treatment of bacterial skin infections.

In more recent experiments, it was possible, in particular, to show that 1-hydroxy-2-pyridones have an uninterrupted spectrum of action against the bacterial species occurring in skin infections, in particular also against antibiotic-resistant strains. In combination with the already-known antimycotic properties of the 1-hydroxy-2-pyridones, this is an extremely important finding for the successful treatment of skin infections, as the hitherto obligatory bacterial identification with subsequent resistance testing on treatment with the substances according to the invention is no longer necessary, which in the end also leads, inter alia, to a substantial reduction in the treatment costs.

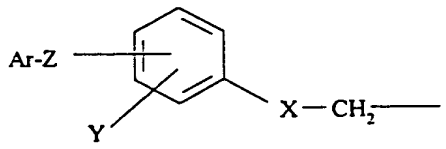
The invention therefore relates to the use of 1-hydroxy-2-pyridones of the formula I



(I)

in which R^1, R^2 and R^3, which are identical or different, are a hydrogen atom or alkyl having 1-4 carbon atoms, and

R^4 is a saturated hydrocarbon radical having 6 to 9 carbon atoms or a radical of the formula II



(II),

where

X is S or O,

Y is a hydrogen atom or up to 2 halogen atoms such as chlorine and/or bromine,

Z is a single bond or the divalent radicals O, S, $-CR^2-$ (R = H or (C_1-C_4)-alkyl) or other divalent radicals having 2-10 carbon and optionally O and/or S atoms linked in the form of a chain, where - if the radicals contain 2 or more O and/or S atoms - the latter must be separated from one another by at least 2 carbon atoms and where 2 adjacent carbon atoms can also be linked to one another by a double bond and the free valencies of the carbon atoms are saturated by H and/or (C_1-C_4)-alkyl groups,

Ar is an aromatic ring system having up to two rings which can be substituted by up to three radicals from the group consisting of fluorine, chlorine, bromine, methoxy, (C_1-C_4)-alkyl, trifluoromethyl and trifluoromethoxy in free or in salt form,

for the production of a pharmaceutical for the topical treatment of skin infections which are caused by fungi and bacteria.

In the radicals "Z", the carbon chain members are preferably CH_2 groups. If the CH_2 groups are substituted by C_1-C_4 alkyl groups, CH_3 and C_2H_5 are preferred substituents. Exemplary radicals "Z" are:

$-O-$, $-S-$, $-CH_2-$, $-(CH_2)_m-$ (m = 2 - 10), $-C(CH_3)_2-$, $-CH_2O-$, $-OCH_2-$, $-CH_2S-$, $-SCH_2-$, $-SCH(C_2H_5)-$, $-CH=CH-CH_2O-$, $-O-CH_2-CH=CH-CH_2O-$, $-OCH_2-CH_2O-$, $-OCH_2-CH_2CH_2O-$, $-SCH_2CH_2CH_2S-$, $-SCH_2CH_2CH_2CH_2O-$, $-SCH_2CH_2OCH_2CH_2O-$, $-SCH_2CH_2OCH_2CH_2O-CH_2CH_2S-$ or $-S-CH_2-C(CH_3)_2-CH_2-S-$.

The radical "S" denotes a sulfur atom, the radical "O" denotes an oxygen atom. The term "Ar" denotes phenyl or condensed systems such as naphthyl, tetrahydronaphthyl and indenyl, and also isolated systems such as those which are derived from biphenyl, diphenylalkanes, diphenyl ethers and diphenyl thioethers.

In the formula I, the hydrocarbon radical R^4 is an alkyl or cyclohexyl radical which can also be bonded to the pyridone ring via a methylene or ethylene group or can contain an endomethyl group. R^4 can also be an aromatic radical which, however, is preferably bonded to the pyridone radical via at least one aliphatic carbon atom.

Important representatives of the class of compound characterized by the formula I are:

6-[4-(4-chlorophenoxy)phenoxymethyl]-1-hydroxy-4-methyl-2-pyridone, 6-[4-(2,4-dichlorophenoxy)phenoxymethyl]-1-hydroxy-4-methyl-2-pyridone, 6-(biphenylyl-4-oxymethyl)-1-hydroxy-4-methyl-2-pyridone, 6-(4-benzyl-phenoxymethyl)-1-hydroxy-4-methyl-2-pyridone, 6-[4-(2,4-dichloro-benzyloxy)phenoxymethyl]-1-hydroxy-4-methyl-2-pyridone, 6-[4-(4-chlorophenoxy)phenoxymethyl]-1-hydroxy-3,4-dimethyl-2-pyridone, 6-[4-(2,4-dichlorobenzyl)phenoxymethyl]-1-hydroxy-3,4-dimethyl-2-pyridone, 6-[4-(cinnamyloxy)phenoxymethyl]-1-hydroxy-4-methyl-2-pyridone, 1-hydroxy-4-methyl-6-[4-(4-trifluoromethylphenoxy)phenoxymethyl]-2-pyridone, 1-hydroxy-4-methyl-6-cyclohexyl-2-pyridone, 1-hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2-pyridone, 1-hydroxy-4-methyl-6-n-hexyl-, -6-iso-hexyl-, -6-n-heptyl- or -6-iso-heptyl-2-pyridone, 1-hydroxy-4-methyl-6-octyl- or -6-iso-octyl-2-pyridone, in particular 1-hydroxy-4-methyl-6-cyclohexyl-methyl- or -6-cyclohexylethyl-2-pyridone, where the cyclohexyl radical in each case can also carry a methyl radical, 1-hydroxy-4-methyl-6-(2-bicyclo[2,2,1]heptyl)-2-pyridone, 1-hydroxy-3,4-dimethyl-6-benzyl- or -6-dimethylbenzyl-2-pyridone or 1-hydroxy-4-methyl-6-(ß-phenylethyl)-2-pyridone.

The term "saturated" here designates those radicals which contain no aliphatic multiple bonds, i.e. no ethylenic or acetylenic bonds. The term "topical" is understood as meaning the local action on the skin. The term "fungus" means all chlorophyll-free cells with cellulose or chitin in the cell walls which contain chromosomes in the cell nucleus. The fungi in particular include yeast, mold fungi, skin, hair and budding fungi. The term "bacteria" means microorganisms with heterotrophic or autotrophic metabolisms, which have no chromosomal nucleus. The bacteria include gram-positive and gram-negative microorganisms, in particular those which can grow on the skin surface of humans or animals, for example skin-pathogenic bacteria of the genera staphylococci, streptococci, corynebacteria, propionibacteria and Proteus, and also other aerobic and anaerobically growing bacteria such as enterococci, Escherichia coli, Pseudomonas and Klebsiella. The term "antibiotic resistance" means the property of microorganisms to be insensitive to the therapeutically achievable active compound concentration of an active compound.

The abovementioned compounds of the formula I can be employed both in free form and as salts; use in free form is preferred.

If organic bases are used, poorly volatile bases are preferably employed, for example low molecular weight alkanolamines such as ethanolamine, diethanolamine, N-ethylethanolamine, N-methyldiethanolamine, triethanolamine, diethylaminoethanol, 2-amino-2-methyl-n-propanol, dimethylaminopropanol, 2-amino-2-methylpropanediol, triisopropanolamine. Further poorly volatile bases which may be mentioned are, for example, ethylenediamaine, hexamethylenediamine, morpholine, piperidine, piperazine, cyclohexylamine, tributylamine, dodecylamine, N,N-dimethyldodecylamine, stearylamine, oleylamine, benzylamine, dibenzylamine, N-ethylbenzylamine, dimethylstearylamine, N-methylmorpholine, N-methylpiperazine, 4-methylcyclohexylamine, N-hydroxyethylmorpholine. The salts of quaternary ammonium hydroxides such as trimethylbenzylammonium hydroxide, tetramethylammonium hydroxide or tetraethylammonium hydroxide can also be used, and

furthermore guanidine and its derivatives, in particular its alkylation products. However, it is also possible to employ, for example, low molecular alkylamines such as methylamine, ethylamine or triethylamine as salt-forming agents. Salts with inorganic cations, for example alkali metal salts, in particular sodium, potassium or ammonium salts, alkaline earth metal salts such as in particular the magnesium or calcium salts, and salts with di- to tetravalent cations, for example the zinc, aluminum or zirconium salt, are also suitable for the compounds to be employed according to the invention.

The active compounds of the formula I to be employed in the preparations can be prepared, for example, by the process according to US 2 540 218.

For use according to the invention of the compounds mentioned, liquid to semisolid pharmaceutical preparations are suitable, in particular solutions, cream, ointment and gel preparations, where the latter are preferably used because of their increased release of active compound. The production of these preparations is carried out in a manner known per se with addition of the active compound employed according to the invention. Of the abovementioned 1-hydroxy-2-pyridones, the preparations according to the invention can contain one compound or alternatively two or more in combination.

In the preparations according to the invention, the active compound is incorporated in amounts which are customarily between approximately 0.1 and approximately 5%, preferably between 0.5 and 1%.

Using the pharmaceuticals according to the invention, a drastic cure can be achieved in the topical treatment of infections of the skin. The compositions according to the invention can also be employed for the treatment of acne, rosacea - a disease of still unclarified etiology - and of erythrasma, a pseudomycosis of the skin caused by Corynebacterium minutissimum.

Example 1

A preparation according to the invention has the following composition:

1-Hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2(1H)pyridone	0.50%
Hydroxyethylcellulose	1.50%
Polyethylene glycol-7 glycerylcocoate	5.00%
1,2-Propylene glycol	10.00%
Isopropyl alcohol	20.00%
Demineralized water	63.00%

Example 2

A preparation according to the invention has the following composition:

1-Hydroxy-4-methyl-6-cyclohexyl-2(1H)pyridone	1.00%
Polyacrylic acid polymer	
(e.g. Carbomer 934 P)	0.70%
Sodium hydroxide	0.20%
Sodium dioctylsulfosuccinate	0.05%
2-Octyldodecanol	7.50%
Isopropyl alcohol	25.00%
Demineralized water	65.55%

Example 3

A preparation according to the invention has the following composition:

1-Hydroxy-4-methyl-6-cyclohexyl-2(1H)pyridone	0.50%
Polyacrylic acid polymer	
(e.g. Carbomer 940)	0.50%
Sodium hydroxide	0.20%
Polyoxyethylene(20) sorbitan monostearate	3.50%
Isopropyl myristate	10.00%
Ethanol	20.00%
Demineralized water	65.30%

Example 4

A preparation according to the invention has the following composition:

1-Hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2(1H)-pyridone	1.00%
Hydroxypropylcellulose	1.00%
1,2-Propylene glycol	2.50%
Ethanol	20.00%
Demineralized water	75.50%

Example 5

A preparation according to the invention has the following composition:

1-Hydroxy-4-methyl-6-cyclohexyl-2(1H)pyridone	1.00%
Isopropyl alcohol	25.00%
Polyethylene glycol 400	5.00%
Demineralized water	69.00%

Example 6

A preparation according to the invention has the following composition:

1-Hydroxy-4-methyl-6-(trimethyl-pentyl)-2(1H)pyridone	1.00%
2-Octyldocenol	5.00%
Liquid paraffin	5.00%
Cetyl alcohol	5.00%
Stearyl alcohol	5.00%
Myristyl alcohol	5.00%
Polyoxyethylene-20-sorbitan monostearate	3.00%
Sorbitan monostearate	2.00%
Demineralized water	69.00%

Example 7

Activity testing

Determination of the antibacterial activity of 1-hydroxy-4-methyl-6-

cyclohexyl-2(1H)pyridone to skin-pathogenic gram-positive and gram-negative aerobic bacteria.

The minimal inhibitory concentration (MIC) was determined in an agar dilution test in Mueller-Hinton agar. The active compound was first dissolved in dimethyl sulfoxide at 10% strength and then diluted to twice the amount in each case in equal stages with agar so that in the end effect concentrations between 128 µg/ml and 1 µg/ml were obtained. Overnight cultures of the bacterial strains to be tested were diluted with liquid medium and employed as inoculum. The bacterial suspensions (1×10^5 cfu/ml) were applied to the surface of the active compound-containing agar plates. With the exception of the methicillin-resistant strains of Staphylococcus aureus (MRSA) and Staphylococcus epidermidis (MRSE), the MIC values were read off after 24 hours at 37°C(MRSA and MRSE: 48 hours at 30°C).

The lowest concentration at which growth was no longer to be observed was designated as the MIC.

Using known methods, the antibiotic-resistant bacteria investigated can be isolated from patients or from hospitals in which antibiotic resistance has been found. The other bacterial species mentioned can be isolated easily by a person skilled in the art on account of their species and generic name or ordered from a strain collection.

Results

In vitro activity of 1-hydroxy-4-methyl-6-cyclohexyl-2(1H)pyridone against aerobic bacteria

Gram-positive strains	n =	MIC (µg/ml) (n =)
Staphylococcus aureus	20	64
S. aureus, methicillin-resistant MRSA	19	64
S. aureus, ofloxacin-resistant, OFX^r	16	$64_{(8)}$, $128_{(8)}$
Staphylococcus epidermidis	20	128
S. epidermidis, methicillin-resistant, MRSE	2	64
S. epidermidis, ofloxacin-resistant, OFX^r	4	64
Streptococcus pyogenes	20	64
Strept. faecalis	3	$64_{(1)}$, $128_{(2)}$
Strept. faecium	1	128
Strept. faecium, vancomycin-resistant, VAN^r	1	32
Strept. durans	10	$64_{(4)}$, $128_{(6)}$
Strept. equisimilis	1	128
Strept. agalactiae	9	128
Gram-negative strains	n =	MIC (µg/ml) (n =)
Proteus vulgaris	3	$32_{(1)}$, $64_{(2)}$
Enterobacter aerogenes	1	128
Enterobacter cloacae	1	128
Escherichia coli	3	64
Klebsiella pneumoniae	2	$64_{(1)}$, $128_{(1)}$
Pseudomonas aeruginosa	5	128

n = number of strains investigated; the number mentioned in brackets gives the tested strains in which the MIC mentioned was determined.

In vitro activity of 1-hydroxy-4-methyl-6-cyclohexyl-2(1H)pyridone against anaerobic bacteria

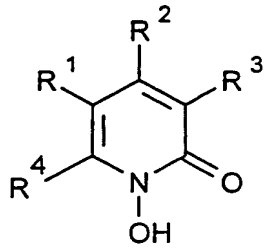
(the testing was carried out in an agar dilution test using Wilkins-Chalgren agar (Oxoid).

Description of bacteria		MIC (µg/ml)
Propionibacterium acnes	Strain 6919	32.0
"	Strain 6922	32.0
"	Strain 15549	32.0
"	Strain DSM 20458	32.0

All bacterial strains tested are inhibited in growth - without exception - in a very narrow concentration range of 1-hydroxy-2-pyridones. This also applies to strains which are resistant against therapy with antibiotics such as methicillin, ofloxacin and vancomycin.

Patent claims:

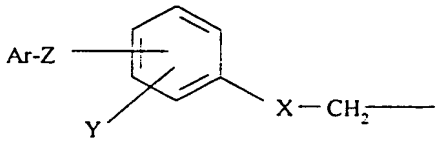
1. The use of 1-hydroxy-2-pyridones of the formula I



(I)

in which R^1, R^2 and R^3, which are identical or different, are a hydrogen atom or alkyl having 1-4 carbon atoms, and

R^4 is a saturated hydrocarbon radical having 6 to 9 carbon atoms or a radical of the formula II



(II),

where

X is S or O,

Y is a hydrogen atom or up to 2 halogen atoms such as chlorine and/or bromine,

Z is a single bond or the divalent radicals O, S, $-CR^2-$ (R = H or (C_1-C_4)-alkyl) or other divalent radicals having 2-10 carbon and optionally O and/or S atoms linked in the form of a chain, where - if the radicals contain 2 or more O and/or S atoms - the latter must be separated from one another by at least 2 carbon atoms and where 2 adjacent carbon atoms can also be linked to one another by a double bond and the free valencies of the

carbon atoms are saturated by H and/or (C_1-C_4)-alkyl groups,

Ar is an aromatic ring system having up to two rings which can be substituted by up to three radicals from the group consisting of fluorine, chlorine, bromine, methoxy, (C_1-C_4)-alkyl, trifluoromethyl and trifluoromethoxy,

for the production of a pharmaceutical for the topical treatment of skin infections which are caused by fungi and bacteria.

2. The use as claimed in claim 1, wherein the compound of the formula I is employed in which Ar is a bicyclic system which is derived from biphenyl, diphenylalkane or diphenyl ether.

3. The use as claimed in claim 1 or 2, wherein the compound of the formula I contains a cyclohexyl radical in the position R^4.

4. The use as claimed in one or more of claims 1 to 3, wherein the compound of the formula I contains an octyl radical of the formula $-CH_2-CH(CH_3)-CH_2-C(CH_3)_3$ in the position R^4.

5. The use as claimed in claim 1, wherein 1-hydroxy-4-methyl-6-[4-(4-chlorophenoxy)phenoxymethyl]-2-(1H)pyridone, 1-hydroxy-4-methyl-6-cyclohexyl-2-(1H)pyridone or 1-hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2-(1H)pyridone is employed.

6. The use as claimed in one or more of claims 1 to 5 for the topical treatment of skin infections which are caused by gram-

positive and/or gram-negative microorganisms, in particular those which can grow on the skin surface of humans or animals.

7. The use as claimed in claim 6 for the topical treatment of skin infections which are caused by skin-pathogenic bacteria from one or more of the genera staphylococci, streptococci, Proteus, corynebacteria and propionibacteria or which are caused by other bacteria which grow aerobically or anaerobically, such as Escherichia coli, enterococci, Pseudomonas or Klebsiella.

8. The use as claimed in one or more of claims 1 to 7, wherein bacterial skin infections are treated which are caused by antibiotic-resistant bacteria.

9. The use as claimed in one or more of claims 1 to 8 wherein acne, rosacea or erythrasma is treated.

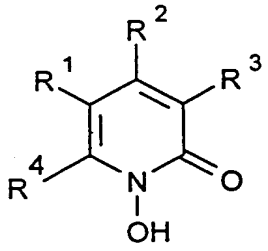
10. The use of the compound of the formula I as claimed in one or more of claims 1 to 5 for the production of a pharmaceutical for the treatment of bacterial skin infections which are caused by antibiotic-resistant bacteria.

11. The use as claimed in claim 10, wherein acne, rosacea or erythrasma is treated.

Abstract

Use of 1-hydroxy-2-pyridones for the treatment of skin infections

Compounds of the formula I



(I)

are suitable for the production of pharmaceuticals for the topical treatment of skin infections which are caused by fungi and bacteria.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 97/05069

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/44

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 31 40 954 A (HEOCHST AG) 5 May 1983 see the whole document	1,3-7,9
X	EP 0 218 410 A (BEECHAM GROUP PLC) 15 April 1987 see the whole document	1,3-7,9
X	GB 2 208 149 A (L'OREAL) 8 March 1989 see abstract see page 3, line 5 - line 12 see page 4 see page 5, line 1 - line 12 see page 9, line 24 - line 25 see claims 17,20	1,3-5,9
X	FR 2 685 638 A (LABORATOIRES BIORGA) 2 July 1993 see the whole document	1,3-7,9

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

Date of the actual completion of theinternational search	Date of mailing of the international search report
15 January 1998	30/01/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gac, G

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 680 745 A (L'OREAL) 8 November 1995 see the whole document	1,3-5
X	HÄNEL: "A comparison of bifonazole and ciclopiroxolamine : in-vitro, animal and clinical studies" MYCOSES, vol. 31, no. 12, 1988, pages 632-640, XP002052266 see the whole document	1,3,5
A	WO 96 13247 A (TRISTATA) 9 May 1996 see abstract see page 9, line 15	9
X	EP 0 646 369 A (HOECHST AG) 5 April 1995 siehe das ganze Dokument, insbesondere Seite 2	1,2,5
X	EP 0 649 660 A (HOECHST AG) 26 April 1995 see abstract see page 5, line 20	1,2,5